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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,002	06/22/2000	Harold Inge Nyland	Q59836	8578

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	14

DATE MAILED: 11/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,002	NYLAND ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Notice to Comply

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I in Paper No. 10 is acknowledged. The traversal is with respect to the restriction of Groups I-III. (The claims of Group IV, claims 33-35, have been canceled.) Upon further consideration, the restriction with respect to Groups I-III is withdrawn. Applicant's election of claim 18, genotype FcγRIIIB NA1/NA1, in paper no. 13, is also acknowledged. It is noted that the species encompassed by claims 18-22 have been examined.

Sequence Listing

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures, and because the specification recites sequences that lack description by a sequence identifier set forth in the "Sequence Listing" as required by 37 CFR § 1.821(d). See, for example, p. 9. Appropriate corrections for compliance are required. Applicant is requested to return a copy of the attached Notice to Comply with the response to this Office action.

Specification

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

4. The specification is objected to because it does not contain, as a separate section, a brief description of the drawings. Amendment of the specification to include a separate section briefly describing the content of each of the drawings, as set forth in 37 CFR 1.74, is required.

This rejection may be overcome by, e.g., amending page 10 of the specification at line 36 such that it recites the heading "Brief Description of the Drawings".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which if pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods in which a genotype of FcγRIIA H/H, FcγRIIIB NA1/NA1 or a combination thereof in a human afflicted with multiple sclerosis is indicative of a benign prognosis, in which a genotype of FcγRIIA R/R, FcγRIIIB NA2/NA2 or a combination thereof in a human afflicted with myasthenia gravis is indicative of a benign prognosis and a genotype of FcγRIIIB NA1/NA1 in such a patient is indicative of a non-benign prognosis, and in which a genotype of FcγRIIA H/H, FcγRIIIB NA1/NA1 or a combination thereof in a human afflicted with diabetes mellitus is indicative of a non-benign prognosis, does not reasonably provide enablement for the practice of the claimed methods in non-human subjects, for methods in which a genotype of FcγRIIIB NA2/NA2 in a patient suffering from cerebrovascular disease, cardiovascular disease or atherosclerosis is indicative of a non-benign prognosis, for

methods in which a genotype of FcγRIIA H/H in a patient afflicted with Addison's disease is indicative of a non-benign prognosis, or for methods in which any Fc receptor genotype, including any Fcγ receptor genotype, is detected in order to determine the prognosis for any of the diseases and conditions recited in claims 15 and 30, other than the specific examples recited above (i.e., those of claims 18-20 in human subjects). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods in which Fc receptor genotypes are determined in a mammalian subject in order to determine the prognosis for a disease selected from multiple sclerosis (MS), myasthenia gravis (MG), diabetes mellitus, cerebrovascular disease, cardiovascular disease, atherosclerosis, and Addison's disease (see claims 15 and 30). It is noted that dependent claims 18-22 are limited to the detection of particular genotypes as prognostic indicators in subjects suffering from particular conditions, but encompass any type of mammalian subject. The specification provides evidence that one of skill in the art would consider the particular genotypes recited in claims 18-20 as one factor contributing to disease prognosis in humans suffering from MS, MG and diabetes, respectively (see Examples 2-3 and 5). However, the specification is silent with respect to any associations between these genotypes and disease prognosis in non-human mammals. With respect to claims 21-22, the data provided in the specification do not demonstrate a significant association between genotype and disease prognosis for Addison's disease or for the diseases recited in claim 21.

Further, the specification is silent with respect to any relationship between the numerous other Fc receptor genotypes and combinations thereof encompassed by the claims and any of the several conditions embraced by claims 15-17 and 23-32 in any type of mammal. Absent guidance from the specification, one of skill in the art may look to the teachings of the prior art for enablement of a claimed invention. In the instant case, the prior art discloses a relationship between FcγRIIIB genotype and prognosis for Wegener's granulomatosis (see Kimberly et al, WO 96/06952 [3/1996]) and neonatal neutropenia (see Bux et al, Blood 89(3):1027-1034 [2/1997]) in humans. However, the prior art is silent regarding other relationships between Fc receptor genotypes and the diseases encompassed by the claims in either humans or non-human mammals. Accordingly, it is unpredictable as to whether such relationships even exist. Given the lack of guidance provided in the specification and in the art, it is therefore unpredictable as to whether any quantity of experimentation would be sufficient to allow one to practice applicants' invention in a manner reasonably commensurate with the claims. While one of skill in the art could practice methods in which a genotype of FcγRIIA H/H, FcγRIIIB NA1/NA1 or a combination thereof in a human afflicted with multiple sclerosis is indicative of a benign prognosis, in which a genotype of FcγRIIA R/R, FcγRIIIB NA2/NA2 or a combination thereof in a human afflicted with myasthenia gravis is indicative of a benign prognosis and a genotype of FcγRIIIB NA1/NA1 in such a patient is indicative of a non-benign prognosis, and in which a genotype of FcγRIIA H/H, FcγRIIIB NA1/NA1 or a combination thereof in a human afflicted with diabetes mellitus

is indicative of a non-benign prognosis, it would require undue experimentation to use invention as now claimed.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 15-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-29 and 32 are indefinite over the recitation of the limitation "determining, as a genetic marker," in claim 15, step (a). It is unclear as to how the recitation "as a genetic marker" is intended to further limit the claims. Specifically, it is unclear how determining a genotype would differ from determining a genotype "as a genetic marker."

Claims 15-32 are unclear because it is unclear as to how the Fc receptor obtained from "a normal mammalian subject" or a "diseased mammalian subject" in claim 15, step (b) and claim 30, step (c), relate to the "at least one Fc receptor" of claim 15, step (a) and claim 30, step (a), respectively. Particularly, it is unclear as to whether the claims are intended to require a comparison of genes encoding the same type of Fc receptor in the test and control subjects, and if not, how one could conclude that the test subject has either a benign or non-benign prognosis when, e.g., genes encoding different types of Fc receptors are compared. Clarification is required.

Claims 16-17 are indefinite over the recitation of the limitation "said Fc receptor" in claim 16. It is unclear as to whether this recitation is intended to refer back to the "at

least one Fc receptor" of claim 15, (a), to the Fc receptor from a normal or diseased subject of claim 15, step (b), or to each of these. Clarification is required.

Claims 23, 27-29 and 31 are indefinite because it is unclear as to how the claims would be further limiting of claim 15 and claim 30 in instances when "the genotype....from a normal mammalian subject" is employed in the claimed method. Claims 23 and 31 require a further step of determining a marker for susceptibility to "said disease;" however, only some embodiments encompassed by the claims employ "said diseased mammalian subject" (see step (b) of claim 15 and step (c) of claim 30). Accordingly, clarification is required with respect to how the claims would further limit methods in which "a normal mammalian subject" is employed in step (b) of claim 15/step (c) of claim 30.

Claims 30-31 are indefinite because it is unclear as to what diagnosis would result from the practice of the claimed "diagnostic method" in instances when the genotype of the "normal mammalian" subject is employed in "comparing" step (c). While claim 30 recites a diagnosis for embodiments of the claims in which the genotype of the "diseased mammalian subject" is employed, it is unclear as to what diagnosis would be reached in the alternative embodiment encompassed by the claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 15-17, 23, 26-27 and 30-32 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kimberly et al (WO 96/06952 [3/1996]).

Kimberly et al disclose methods of diagnosing "predisposition to severe forms of autoimmune disease" comprising steps of determining patterns of Fcγ receptor alleles in a patient and comparing those patterns to control patterns characterizing populations free of disease and/or having disease of different levels of severity in order to determine the patient's prognosis (see entire reference, especially, e.g., page 4). The methods disclosed by Kimberly et al include methods in which predisposition to "severe forms" of Wegener's granulomatosis is determined by identifying a patient's pattern of Fcγ RIIIB alleles (p. 4). It is an inherent property of Wegener's granulomatosis that it characterized by systemic vasculitis and constitutes a type of "cardiovascular disease." Kimberly et al provide evidence that Fcγ RIIIB genotype NA1/NA1 is more prevalent in Wegener's patients than in a normal population (see Example 6). Regarding claims 26-27, Kimberly et al disclose further steps of administering agents that constitute "prophylactic or therapeutic" materials to patients having a non-benign prognosis (see, e.g., p. 6). Regarding claim 32, it is noted that the methods employed by Kimberly et al employ allele-specific probes (see Example 6). Accordingly, Kimberly et al anticipate claims 15-17, 23, and 30-32.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimberly et al (WO 96/06952 [3/1996]) in view of Herridge et al (Journal of Thoracic and Cardiovascular Surgery 111(5):961-966 [5/1996]).

Kimberly et al disclose methods of diagnosing "predisposition to severe forms of autoimmune disease" comprising steps of determining patterns of Fcγ receptor alleles in a patient and comparing those patterns to control patterns characterizing populations free of disease and/or having disease of different levels of severity in order to determine the patient's prognosis (see entire reference, especially, e.g., page 4). The methods disclosed by Kimberly et al include methods in which predisposition to "severe forms" of Wegener's granulomatosis is determined by identifying a patient's pattern of Fcγ RIIIB alleles (p. 4). It is a property of Wegener's granulomatosis that it characterized by systemic vasculitis and constitutes a type of "cardiovascular disease." Kimberly et al provide evidence that Fcγ RIIIB genotype NA1/NA1 is more prevalent in Wegener's

patients than in a normal population (see Example 6). Kimberly et al disclose further steps of administering agents that constitute "prophylactic or therapeutic" materials to patients having a non-benign prognosis (see, e.g., p. 6), and that determination of prognosis is useful in facilitating "the choice of appropriate therapeutic interventions" for a patient (p. 3). However, Kimberly et al do not disclose surgical intervention as a treatment for Wegener's granulomatosis. Herridge et al teach that surgery such as tracheal reconstruction is appropriate treatment for some symptoms of Wegener's granulomatosis (see entire reference, especially p. 962 and 964). In view of the teachings of Herridge et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kimberly et al so as to have included a further step of surgical intervention following determination of a non-benign prognosis in cases of Wegener's granulomatosis involving subglottic stenosis. An ordinary artisan would have been motivated to have made such a modification for the advantage of improving the quality of life and functional status of these individuals, as suggested by Herridge et al (see p. 964).

14. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kimberly et al in view of Bux et al (Blood 89(3):1027-1034 [2/1997]).

Kimberly et al disclose methods of diagnosing "predisposition to severe forms of autoimmune disease" comprising steps of determining patterns of Fcγ receptor alleles in a patient and comparing those patterns to control patterns characterizing populations free of disease and/or having disease of different levels of severity in order to determine the patient's prognosis (see entire reference, especially, e.g., page 4). The methods

disclosed by Kimberly et al include methods in which predisposition to "severe forms" of Wegener's granulomatosis is determined by identifying a patient's pattern of Fcγ RIIIB alleles (p. 4). It is a property of Wegener's granulomatosis that it characterized by systemic vasculitis and constitutes a type of "cardiovascular disease." However, Kimberly et al provide evidence that Fcγ RIIIB genotype NA1/NA1 is more prevalent in Wegener's patients than in a normal population (see Example 6), whereas claim 21 requires that the presence of Fcγ RIIIB genotype NA2/NA2 is indicative of "a non-benign prognosis." Bux et al disclose that the NA2/NA2 genotype is associated with neutropenia in some individuals (see entire reference, especially p. 1027 and 1031), and that neutropenia may trigger cerebral hemorrhage, a type of "cerebrovascular disease" (see p. 1027-1028). In view of the teachings of Bux et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kimberly et al so as to have detected the presence of an NA2/NA2 genotype in a neonate as an indicator of the "non-benign" prognosis of increased risk for neonatal neutropenia as compared to a neonate with, e.g., an NA-null genotype, as discussed on p. 1027 of Bux et al. An ordinary artisan would have been motivated to have made such a modification for the advantage of rapidly assessing relative risk of neutropenia and possible cerebrovascular complications thereof in a newborn.

15. Claims 24 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimberly et al in view of Bux et al as applied to claim 21, above, and further in view of Van Nostrand et al (U.S. Patent No. 5,270,165 [12/1993]).

The combined references of Kimberly et al and Bux et al do not suggest a further step of subjecting the test subject to diagnostic imaging, as required by claims 24 and 28. Van Nostrand et al disclose that cerebral hemorrhage is diagnosed by imaging methods such as "computerized tomography and nuclear magnetic resonance imaging" (col 28, lines 54-57). In view of the teachings of Van Nostrand et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kimberly et al in view of Bux et al so as to have included a step of diagnostic imaging. An ordinary artisan would have been motivated to have made such a modification for the advantage of rapidly detecting cerebral hemorrhage or confirming the presence of a suspected cerebral hemorrhage in a neonate suffering from neutropenia.

Conclusion

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
November 4, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600